The amendment filed 16 January 2008 is acknowledged and has been entered. Claim 48 has been cancelled. Claims 39-47 and 49-55 remain in the case.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claim 40 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons of record as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809. Applicant specifically claims and/or requires the 3B10, 4B2, 10, 17, 24, 25, 26, 27, 31, 41, 50, 60, 87, 3-4A, and 3-11F antibodies.

The specification is objected to and claims 39-47, 49-51, and 53-55 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons of record as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the biological materials required by the claims are: (1) known and readily available to the public; (2) reproducible from the written description; or,

(3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809. Applicant's disclosure teaches that the AL1 and either of the AL12 or AL13 antibodies are required to determine if one has an antibody reacting to any of the other epitopes of a pleiotrophin protein classed by applicant as "type III" (see e.g. page 18).

Applicant's arguments filed 16 January 2008 have been fully considered but they are not deemed to be persuasive.

Applicant's offer to deposit the hybridomas is noted. However, the offer does not clearly state that all the proper conditions, assurances, and corroborations to satisfy the criteria set forth in 37 CFR §§ 1.801-1.809 regarding the deposits will be complied with within the required time. The rejections are maintained.

Claims 40, 46, 47, and 52 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate with that as claimed.

Applicant's arguments filed 16 January 2008 have been fully considered but they are not deemed to be persuasive.

Applicant urges that a limitation to antibody structure is inconsistent with the Written Description Guidelines. This is not found persuasive for a number of reasons. Firstly, it is the

invention as instantly claimed, and not the examiner, that limits the claimed subject matter to particular structures. As set forth, other than antibodies comprising all of the relevant complementarity determining regions (CDRs) of SEQ ID NOS: 3 and 8 disclosed by applicant (SEQ ID NOS: 5-7 and 10-12) in the proper site on an appropriate antibody heavy or light chain framework, respectively, the skilled artisan cannot envision the detailed structure of the full scope of the encompassed polypeptides as are claimed. Applicant has provided no guidance as to what modifications can be made to any one or all of the disclosed CDRs which predictably preserve the function of an antibody for pleiotrophin binding and neutralization. Therefore, notwithstanding applicant's assertions to the contrary, applicant has provided no structure/function correlation and the state of the art is such that one cannot readily envision antibody structures which possess only one, or even several, of the CDRs or only one CDR with 90% sequence identity to one of the CDRs as claimed which predictably bind or do not bind the antigen, let alone those that predictably exhibit neutralizing activities. A generic statement which defines a genus of molecules by only their functional activity has been held by the court, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), to not provide an adequate written description of the genus. Moreover, not knowing, absent further experimentation, which of the single or several CDRs specifically claimed, or modifications thereof, function with which other CDRs and which do not, when, as set forth, even a single change of an amino acid can unpredictably affect structure and antigen-binding function, leads to one having no predictability or expectation of success for the function of any given antibody modification not including all of the disclosed CDRs in the proper site on an appropriate antibody heavy or light chain framework. Such random experimentation to identify at a later

time what structure or modification is or is not functional and is embraced by applicant's claims is undue experimentation. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* (18 USPQ 2d 1027 (CAFC 1991)). As set forth, claims not containing elements critical or essential to the practice of the invention, such as antibodies or antibody fragments having all of the relevant functional complementarity determining regions (CDRs) in the proper site on an appropriate antibody heavy or light chain framework, are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-47, 49-51, and 53-55 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 39 and claims dependent thereupon, it is not clear what applicant intends as encompassed by a "biological activity" of pleiotrophin.

Claim 40 is vague in the absence of recitation of deposit accession number(s) to clearly identify the claimed antibody/hybridoma species because, absent the recitation of deposit accession numbers, it is not clear what structure and properties are encompassed by the named

antibodies. In this claim it is not clear what applicant intends as encompassed by "substantially" the same epitope. What degree of binding reduction is sufficient for "substantial" binding competition? In this claim "the monoclonal antibody" of (a) lacks antecedent basis, perhaps (a) and (b) should be presented in reverse order to provide antecedent basis.

In claims 42-45, it is not clear what is being further limited other than the intended use of the antibody.

In claim 55, "said PTN" protein lacks antecedent basis.

Applicant's arguments filed 16 January 2008 have been fully considered but they are not deemed to be persuasive.

Applicant urges that the examples of therapeutic uses of anti-pleiotrophin antibodies provide a clear description of the term "biological activity." This is not found persuasive because the examples of activities to be inhibited include only a sampling of activities and do not provide an explicit definition of what is meant or encompassed by the term.

Applicant urges that the definition of "substantially the same epitope" would guide one to an understanding of the subject matter claimed. This is not found persuasive for the reasons of record that the degree of binding reduction sufficient for "substantial" binding competition is not clear. Moreover, the encompassed subject matter is not clearly defined because it is well known in the art that antibodies need not bind to the same or overlapping epitope to affect binding of another antibody to a different epitope altered by the binding of the first antibody.

Applicant urges that the "functional" recitations in claims 42-45 further limit the antibody of claim 39 which may not have the desired functions. This is not found persuasive for the reasons of record because the recitations are of intended uses or intended therapeutic results, are

related to cancer cell properties, and are not clearly related to any specific biological activities of PTN neutralized by the antibody.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,
except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language;

Claim 52 is rejected under 35 U.S.C. § 102(e)(1) as being clearly anticipated by Jakobovits et al. (US 2002/0173629). Antibodies comprising the chains of either of SEQ ID NOs: 60 or 64 of the reference comprises SEQ ID NO: 11 as instantly claimed.

Claim 55 is rejected under 35 U.S.C. § 102(e)(2) as being clearly anticipated by Paliard et al. (US 6,562,346) for reasons of record.

Applicant's arguments filed 16 January 2008 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute. Notwithstanding applicant's assertions to the contrary, the reference clearly teaches fusion proteins comprising epitopes from different proteins, albeit from the same virus.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c ) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 39-46, 49, 50, and 53-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Jäger et al. (Int. J. Cancer 73: 537, 1997), Rauvala (EMBO J. 8: 2933, 1989), Ledoux et al. (J. Histochem. Cytochem. 45: 1239, 1997), Harlow et al., Knight (US 5,675,063), and Czubayko et al. (J. Biol. Chem. 269: 21358, 1994).

Jäger et al. teach a polyclonal antibody to pleiotrophin, raised in rabbits by the method of Rauvala, which inhibits the biological activity of the protein. As taught in Rauvala, the antibody was raised by immunization with the N-terminal peptide of pleiotrophin (see page 2934).

Ledoux et al. teach polyclonal antibodies to recombinant pleiotrophin raised in rabbits.

Harlow et al. teach that, once the amino acid and/or nucleic acid sequences of a protein are known, it is routine and conventional in the art to elicit antibodies to peptides and/or fusion proteins derived from the protein and/or to prepare a bank of site-specific monoclonal antibodies for a variety of uses such as functional and clinical studies (pages 72-77). Harlow et al further teach rationales for the selection of synthetic peptides as immunogens (pages 72-77).

Knight teaches the 240E cell line as a fusion partner generally for producing rabbit monoclonal antibodies to a predetermined immunogen. Rabbit antibodies are desirable because such can be elicited to many antigens that are not especially immunogenic in mice, and rabbit antibodies are generally of higher affinity than mouse antibodies. Antibody binding to antigens can be detected by enzyme-linked immunosorbent assay or immunofluorescence. It is desirable to have the fusion partner and the cells to be fused from the same animal species, such as rabbit-rabbit.

Czubayko et al. (see e.g. page 21361, col. 1) desire antibodies as a specific drug for blocking the growth factor activity of pleiotrophin.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited monoclonal antibodies to any epitope of a pleiotrophin protein, particularly to peptides comprising the N-terminal sequence as taught in Rauvala or Jäger et al., or to the entire recombinant protein as taught in Ledoux, or to fusion proteins as taught generally in Harlow et al., because the pleiotrophin proteins are of unquestioned clinical interest, it is conventional in the art to elicit antibodies to sequenced proteins for a variety of uses as taught in Harlow et al., in particular Czubayko et al. desired antibodies as a specific drug for blocking the growth factor activity of pleiotrophin, and one of ordinary skill in the art would

have had a reasonable expectation of success and obvious motivation for generating rabbit monoclonal antibodies reactive with pleiotrophin proteins for use as a blocking agent in view of Jäger et al. or Czubayko et al. due to the teachings that rabbit antibodies are generally of higher affinity than mouse antibodies (Knight), that the peptide of Rauvala or Jäger et al. elicits antibodies in rabbits which bind to and block the native protein and this domain of the protein is exposed for binding as exemplified by the antibodies elicited in Rauvala or Jäger et al., that blocking antibodies were expected from the teachings of Czubayko et al., and that immunization of rabbits with various immunogens, in conjunction with notoriously old and well known fusion techniques and a rabbit fusion partner, achieves the expected result, i.e. the production of rabbit monoclonal antibodies reactive with the immunogenic antigens (Knight). One would have had obvious motivation to have generated monoclonal antibodies in order to provide a potentially unlimited source of homogeneous reagent.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 39-46, 49, 50, and 53-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Jäger et al. (Int. J. Cancer 73: 537, 1997), Rauvala (EMBO J. 8: 2933, 1989), Ledoux et al. (J. Histochem. Cytochem. 45: 1239, 1997), Harlow et al., Roes et al. (J. Immunol. Meth. 183:231-237, 1995), Amet et al. (Mol. Cell. Neurosci. 17:1014, 2001), and Czubayko et al. (J. Biol. Chem 269: 21358, 1994).

Jäger et al. teach a polyclonal antibody to pleiotrophin, raised by the method of Rauvala, which inhibits the biological activity of the protein. As taught in Rauvala, the antibody was raised by immunization with the N-terminal peptide of pleiotrophin (see page 2934).

Ledoux et al. teach polyclonal antibodies to recombinant pleiotrophin.

Harlow et al. teach that, once the amino acid and/or nucleic acid sequences of a protein are known, it is routine and conventional in the art to elicit antibodies to peptides and/or fusion proteins derived from the protein and/or to prepare a bank of site-specific monoclonal antibodies for a variety of uses such as functional and clinical studies (pages 72-77). Harlow et al further teach rationales for the selection of synthetic peptides as immunogens (pages 72-77).

Amet et al. teach pleiotrophin knockout mice.

Roes et al. teach immunization of knockout mice with the knockout gene product for production of monoclonal antibodies.

Czubayko et al. (see e.g. page 21361, col. 1) desire antibodies as a specific drug for blocking the growth factor activity of pleiotrophin.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited monoclonal antibodies in the pleiotrophin knockout mice as taught in Amet et al. to any epitope of a pleiotrophin protein, particularly to peptides comprising the N-terminal sequence as taught in Rauvala or Jäger et al., or to the entire recombinant protein as taught in Ledoux, or to fusion proteins as taught generally in Harlow et al., because the pleiotrophin proteins are of unquestioned clinical interest, it is conventional in the art to elicit antibodies to sequenced proteins for a variety of uses as taught in Harlow et al., in particular Czubayko et al. desired antibodies as a specific drug for blocking the growth factor activity of

pleiotrophin, and one of ordinary skill in the art would have had a reasonable expectation of success and obvious motivation for generating monoclonal antibodies reactive with pleiotrophin proteins for use as a blocking agent in view of Jäger et al. or Czubayko et al. due to the teachings that the peptide of Rauvala or Jäger et al. elicits antibodies which bind to and block the native protein and this domain of the protein is exposed for binding as exemplified by the antibodies elicited in Rauvala or Jäger et al., that blocking antibodies were expected from the teachings of Czubayko et al., and that immunization of knockout mice with various immunogens, in conjunction with notoriously old and well known fusion techniques, achieves the expected result, i.e. the production of monoclonal antibodies reactive with the immunogenic antigens for which the knockout mice have been made deficient (Roes et al.). One would have had obvious motivation to have generated monoclonal antibodies in order to provide a potentially unlimited source of homogeneous reagent.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Applicant's arguments filed 16 January 2008 with regard to the reference of Jäger et al. have been fully considered but they are deemed to be moot in view of the new ground(s) of rejection set forth above.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Papadimitriou et al. (Biochem. Biophys. Res. Comm. 282, 306, 2001) teach the role of an N-terminal peptide of pleiotrophin in angiogenesis.

Dreyfus et al. (Int. J. Dev. Biol. 42: 189, 1998) teach monoclonal anti-pleiotrophin antibodies.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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